Birth cohort effects in neurological diseases: amyotrophic lateral sclerosis, Parkinson's disease and multiple sclerosis

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Abstract: Background: Generational differences in disease rates are the main subject of age-period-cohort (APC) analysis, which is mostly applied in cancer and suicide research. This study applied APC analysis to selected neurological diseases: amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD) and multiple sclerosis (MS). Methods: The analyses were based on Swiss mortality data. Age-stratified data has been available for MS, PD and ALS since 1901, 1921, and 1942, respectively. APC analysis was performed within the framework of logit models. Main effect models were extended by implementing nested effects, i.e. age effects nested in subperiods, in order to account for the fact that age profiles may change for reasons other than generational influences. Results: In preliminary analyses, APC analysis yielded noteworthy birth cohort effects in all three diseases. After implementing nested effects, the birth cohort effects disappeared in ALS, and smoothed out in PD, where they were greater for the generations born before the 1920s. In MS, the birth cohort effects remained stable, and exhibited a peak in cohorts born in the 1910s and 1920s. Conclusions: APC analysis yielded some evidence for birth cohort effects, i.e. predisposing risk factors that may change in historical terms, in MS and PD, but probably not in ALS.

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Birth Cohort Effects in Neurological Diseases: Amyotrophic Lateral Sclerosis, Parkinson's Disease and Multiple Sclerosis

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Key Words

Amyotrophic lateral sclerosis · Parkinson's disease · Multiple sclerosis · Birth cohorts · Statistical methods · Switzerland

Abstract

Background: Generational differences in disease rates are the main subject of age-period-cohort (APC) analysis, which is mostly applied in cancer and suicide research. This study applied APC analysis to selected neurological diseases: amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD) and multiple sclerosis (MS). ***Methods:*** The analyses were based on Swiss mortality data. Age-stratified data has been available for MS, PD and ALS since 1901, 1921, and 1942, respectively. APC analysis was performed within the framework of logit models. Main effect models were extended by implementing nested effects, i.e. age effects nested in subperiods, in order to account for the fact that age profiles may change for reasons other than generational influences. ***Results:*** In preliminary analyses, APC analysis yielded noteworthy birth cohort effects in all three diseases. After implementing nested effects, the birth cohort effects disappeared in ALS, and smoothed out in PD, where they were greater for the generations born before the 1920s. In MS, the birth cohort effects remained stable, and exhibited a peak in cohorts born in the 1910s and 1920s. ***Conclusions:*** APC analysis yielded some evidence for birth cohort effects, i.e. predisposing risk factors that may change in historical terms, in MS and PD, but probably not in ALS.

Introduction

In many chronic diseases, predisposing risk factors can occur long before the onset of the disease. A change in major predisposing risk factors is typically represented by generational change, or, in technical terms, by birth cohort effects, whereas immediate effects of change are denoted by period effects. Birth cohort effects have important implications regarding disease concepts and research strategies. They provide unequivocal evidence that exogenous risk factors can be encountered early in life resulting in a predisposition to a chronic disease. Therefore, etiopathogenetic concepts need to include latency or vulnerability mechanisms. Moreover, birth cohort effects carry the promise of finding direct clues as to relevant risk factors, and of introducing prevention measures in childhood or teenage years.

Age-period-cohort (APC) analysis is the conventional analytical approach for deriving birth cohort effects from any kind of incidence, prevalence or mortality data. APC analysis has a long tradition in epidemiology [1, 2], nota-

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blywith regard to cancer [3, 4], and suicide research [5–7]. However, it has been largely overlooked in neuroepidemiology. In this study we applied APC analysis to data from three neurological diseases, i.e. amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD) and multiple sclerosis (MS).

This study is a replication of the descriptive analysis of ALS, PD and MS carried out 25 years ago by Li et al. [8]. We appreciated the comparative approach and took the opportunity to shed light on these three neurological diseases with a contemporary statistical analysis. In MS, the APC approach has been applied to Swedish data [9], Spanish data [10], regional Norwegian data [11], and a preliminary Swiss study [12], mostly providing evidence for birth cohort effects. To the best of our knowledge, no APC studies have been published with regard to ALS and to PD.

Nevertheless, ALS, PD and MS seem to be promising candidates for detecting birth cohort effects. Firstly, several studies have argued for an increase in incidence and mortality rates from MS [13], ALS [14–18], and PD [19–21] in Western countries during the second half of the last century. Whether the trends in the time series might be due to predisposing factors, or, rather, to immediate factors (such as change of registration practice), is an issue open to further analysis. Secondly, findings such as the seasonality of birth in ALS [22] and MS [23] have suggested that predisposing risk factors might play a role in the etiopathogenesis of these diseases. In both instances, the evidence is indirect, and there have also been conflicting results. In PD, the encephalitis lethargica epidemics of the 1920s has been discussed as a possible source of increased birth cohort risk for developing this disease [24], which has led to several descriptive studies [19, 25].

This study is based on ALS, PD and MS figures displayed in Swiss mortality data. In ALS [26], MS [27–29], and PD [30] the registration level may be assumed to be quite high and to cover 60–90% of all patients. Of these, the percentage registered as underlying cause of death was 88% in ALS [21], between 64% [21] and 83% [31] in MS, and 56% in PD [21].

The registration practice may have changed over intervening decades, thus contributing to period effects but not to birth cohort effects. However, if for some reason the change did not take place for all age groups in parallel [10], new age profiles might have emerged which mimic birth cohort effects. Accordingly, we implemented a nested approach in APC analysis to account for changing age profiles over the 20th century.

Materials and Methods

Data

Swiss mortality data is collated and published by the Federal Statistical Office in Bern. Systematic death certification in Switzerland began in 1876, and is based on certificates that are completed by physicians [32]. Since 1969, the data has been stored on individual computerized records, and more detailed analyses have been possible, including causes of death registered as 'additional' or 'concomitant'. New classifications of the Swiss Federal Statistical Office followed in the periods 1901–1920, 1921–1930, 1931–1941, 1942–1950, 1951–1967, 1968–1994 (ICD8), and since 1995 (ICD10). ALS has been registered since 1942, PD since 1921, and MS since 1901.

With the introduction of the ICD10 coding in 1995, the number of additional causes of death (apart from the underlying cause) was extended from two to three causes. This implies that the proportion of assessed deaths may vary not only as to the cause of death, but also may change with time. In this study, only cases registered as underlying causes of death were included in the calculations documented below.

For the analyses, the data was aggregated into 10-year age and period intervals. The sex- and age-specific population data were derived from Swiss census data (a census every 10 years since 1880).

Methods

APC analysis is usually based on periodically (e.g. annually) collected age-stratified data pooled in so-called cohort tables [33]. The aim of APC analysis is to disentangle the different effects of age (age effects), historical circumstances (period effects), and generational succession (birth cohort effects). It is noteworthy, that in analyses using cohort tables with equal age and period intervals, the birth cohorts are represented directly by the diagonals.

APC models may be built up on variance analytic models and, similarly, on log-linear models [34]. Log-linear models are a variant of general linear models and are applied to categorical (cross-tabulated) data instead of continuous data. The underlying concepts are the same (main effects, interaction effects, nested effects, etc.). To be more specific, in this study we used logit analysis, which is a regression-like extension of log-linear models. The results of logit analysis are identical with results from logistic regression, if the latter includes only categorical variables. The common APC model with A, P and C main effects has the form:

$$\ln(d_{ij}/N_{ij}) = \mu + \alpha_i + \beta_j + \gamma_k,$$

with

$$\Sigma\alpha_i = \Sigma\beta_j = \Sigma\gamma_k = 0,$$

where d_{ij} = number of deaths in the ij-th cell, N_{ij} = population at risk, μ = overall effect, and α_i, β_j, γ_k = age, period, and cohort effects.

In the case of systematically changing age profiles, interaction terms may be required to improve the model fit and, at the same time, to challenge the preliminary results of the main-effect APC model. Interaction effects were implemented in the APC analysis by means of nested effects. In nesting, we consider one or more cell groups within an effect type separately, imbedding therein

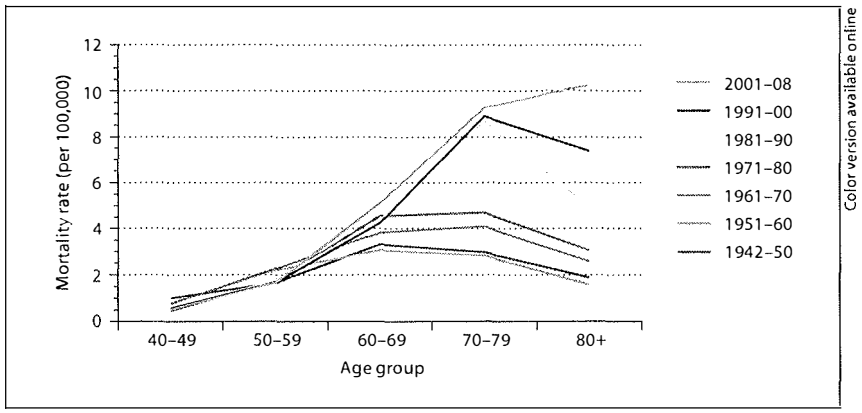

Fig. 1. Age-specific ALS mortality rates, Switzerland, 1942–2008, by decennium.

the effects of another effect type. In APC analysis this means that one of the APC effects is nested within another (e.g. study by Tango and Kurashina [35]). In this study, we nested age effects within subperiods, thus arriving at an A(p)PC model:

$$\ln(d_{ij}/N_{ij}) = \mu + \alpha_i^{(m)} + \beta_j + \gamma_k,$$

with:

$$\Sigma\beta_i = \Sigma\gamma_k = 0$$

$$\Sigma\alpha_i^{(m)} = 0,\ m = 1, \ldots, M,$$

where $\alpha_i^{(m)}$ = age effects nested in m period partitions.

APC analysis is, furthermore, hampered by the redundancy between linear age, period and cohort effects: any two of the three dimensions age, period and cohort determine the third dimension – the so-called identification problem in APC analysis. A simultaneous estimation of all three linear effects is not feasible without arbitrary additional model constraints [36]. Since no solution seems close at hand for the identification problem in APC analysis, a pragmatic procedure was chosen. Given that the age main-effect model typically provided a better fit than analogous period and cohort main-effect models, age was implemented as a mandatory component, and, also, as the target factor for subsequent constraints. Preliminary age (A) models served to derive an estimate for the first age group (and, similarly, each first age group in nested models), which was then used as a constraint in the full APC model.

The model selection in APC analysis is largely data driven and relies mostly on the goodness of fit of the models. This is given by the deviance, i.e. the likelihood ratio χ^2 statistics and the degrees of freedom (d.f.). We typically compared the goodness of fit of AP, A(p)P, APC and A(p)PC models. The aim was to find the most parsimonious model fulfilling the condition that additional effects do not substantially improve the goodness of fit.

The estimates of the A, P and C effects which are reported in the figures are basically defined as deviations from mean = 0; that is, from 1 after exponential transformation. In the 'Results' section, we first discuss the goodness of fit in order to select a model, and then deal with the estimates of the A, P, C and nested effects.

All analyses were carried out using the PROC CATMOD procedure of the SAS statistical package.

Results

Within the period 1942–2008 there were 5,027 deaths with ALS registered as the underlying cause of death. For PD there were 17,544 deaths registered within the period 1921–2008, and for MS, 9,101 cases within the period 1901–2008. Since 1969, when individual computerized records began, the proportion of cases registered as additional cause of death has been 13.4% in ALS, 64.7% in PD and 23.3% in MS.

The graphic displays show two shifts in the age profiles of ALS (fig. 1) and PD (fig. 2) mortality rates. In contrast, the age profiles for MS have changed stepwise in shifts during the 20th century. The longitudinal representation of the age profiles (fig. 3) makes it clear that the monotonic increase in MS rates at the beginning and end of the century was replaced by a curvilinear pattern in intermediate periods.

The model selection in APC analysis turned out to be most difficult in ALS data. Both the main effect APC model (fig. 4, dashed line; deviance 15.0, d.f. 10) and the nested A(p)PC model (deviance 19.8, d.f. 6) worked similarly well. However, they did not provide a clear improvement as compared with the more parsimonious A(p)P model (deviance 25.5, d.f. 12). Thus, it seems unlikely that cohort effects play an important role in ALS. From this standpoint, the nested age effects represent two steps of change in age patterns in ALS mortality. Instead of the curvilinear pattern from the mid 20th century we see a steep increase at the end of the century. Including nested effects led to the period effects pattern becoming reversed and at the same time smoother.

Model selection in the APC analysis of PD data (fig. 5) clearly pointed to the A(p)PC model, whose fit (deviance

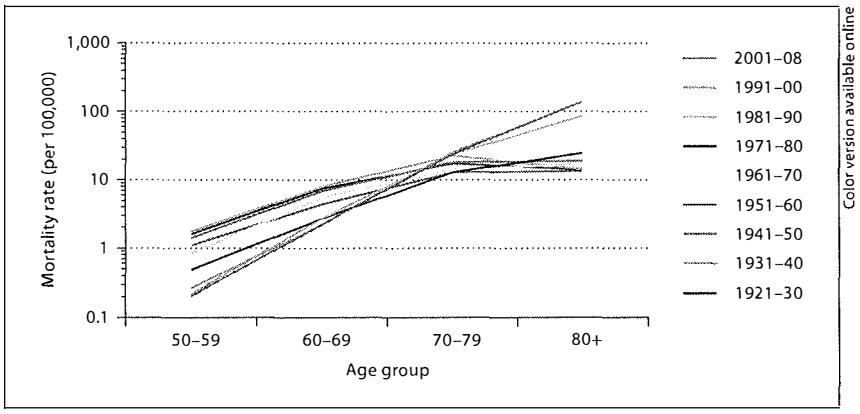

Fig. 2. Age-specific PD mortality rates, Switzerland, 1921–2008, by decennium.

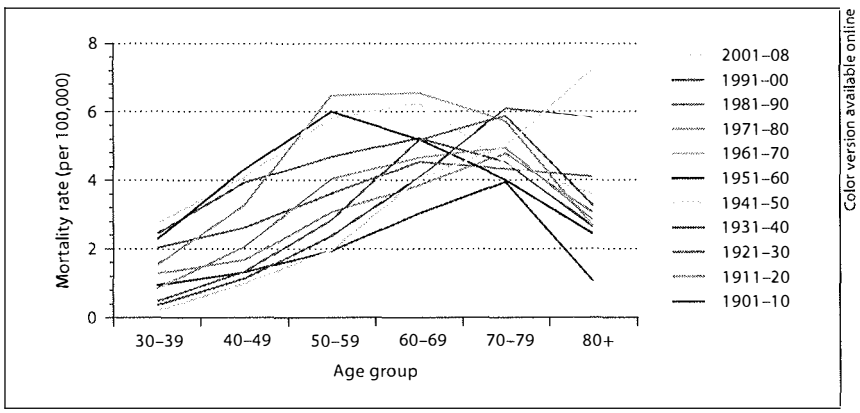

Fig. 3. Age-specific MS mortality rates, Switzerland, 1901–2008, by decennium.

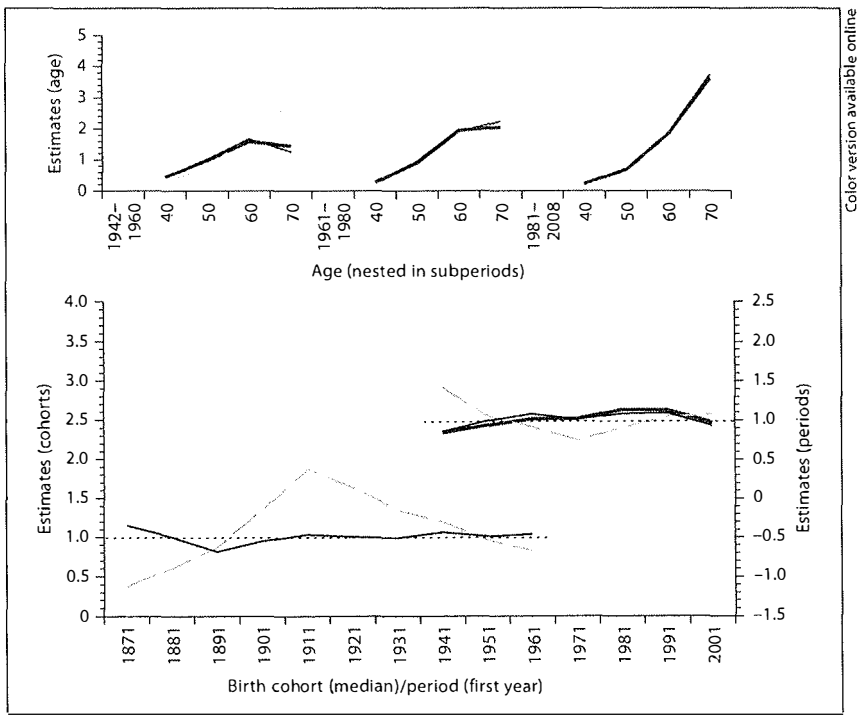

Fig. 4. APC analysis of Swiss ALS mortality data, 1942–2008: estimates of the main effect APC model (dashed line), the A(p)P model including nested effects (bold line) and the A(p)PC model including nested effects (thin line). The A and P estimates of the latter models overlay each other since they are almost identical.

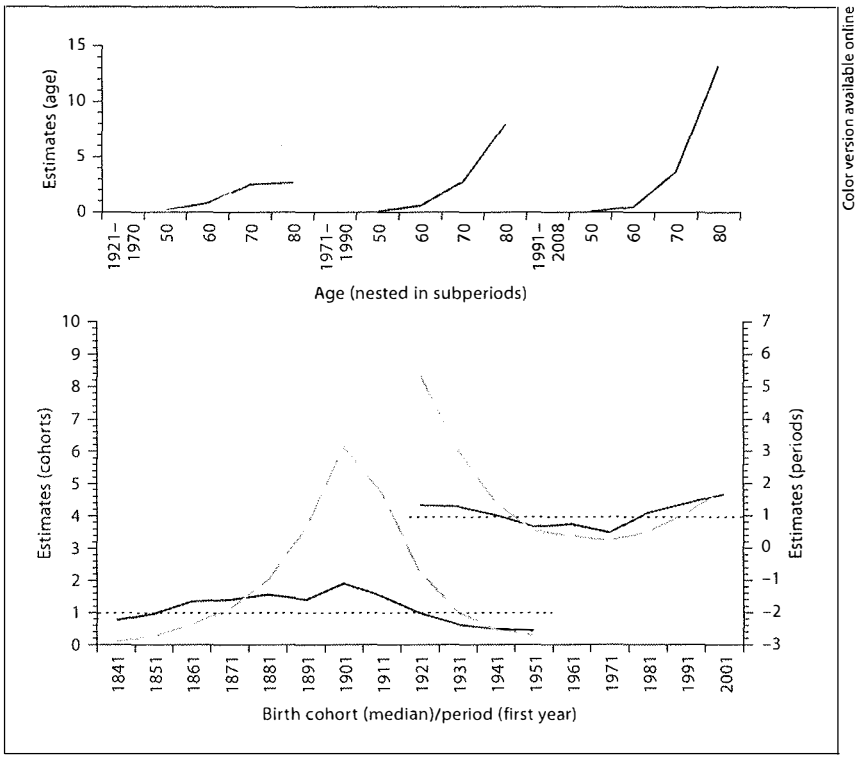

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Fig. 5. APC analysis of Swiss PD mortality data, 1921–2008: estimates of the main effect APC model (dashed line) and the A(p)PC model including nested effects (bold line).

62.5, d.f. 10) was superior to that of the APC model (deviance 108.3, d.f. 14) and other models. Just as with ALS, the age patterns became steeper in the second half of the 20th century and ended up with a steep increase around 2000. As another parallel, the period and birth cohort estimates smoothed out in the nested model; however, they did not change patterns. The period estimates indicate that PD mortality increased in the 1920–1930s and later since the 1990s. In addition, the analysis showed that birth cohorts born between 1870 and 1920 lived with an increased risk of developing PD.

In MS (fig. 6), the comparison of model fits favored the main effect APC model (deviance of 36.7 with d.f. 27) over the A(p)PC model [deviance of 39.0 with d.f. 21 (and 3 fixed estimates instead of 1)]. Moreover, the period and birth cohort estimates did not smooth out as with ALS and PD. The period estimates were low at the beginning of the 20th century, and, after an intermediate period, have decreased markedly since the 1960s. Finally, the birth cohorts carrying an enhanced risk of MS were born between 1890 and 1930, with the peak occurring in Switzerland around 1910–1920.

Discussion

This study examined birth cohort effects in three neurological diseases (ALS, PD, MS) by means of APC analysis extended by nested effects. The analyses were based on Swiss mortality data. Birth cohort effects in ALS were ambiguous, and could be putatively replaced by nested effects (age effects nested in periods). In PD, the effects were increased in cohorts born before the 1920s. Finally, we found distinct and stable birth cohort effects in MS with a peak occurring around the years 1910–1920.

Amyotrophic Lateral Sclerosis

The etiopathogenetic hypotheses regarding ALS pathogenesis sometimes include the mechanism of predisposing risk factors, and a latency period, for example following the polio model [37]. However, full APC analyses have not yet been applied in the epidemiology of ALS. The descriptive study by Li et al. [8] found some evidence for birth cohort effects from descriptive analyses of UK mortality data. Moreover, several analyses of the age structure sought to show whether changes in ALS incidence/mortality are real, or have an artificial background,

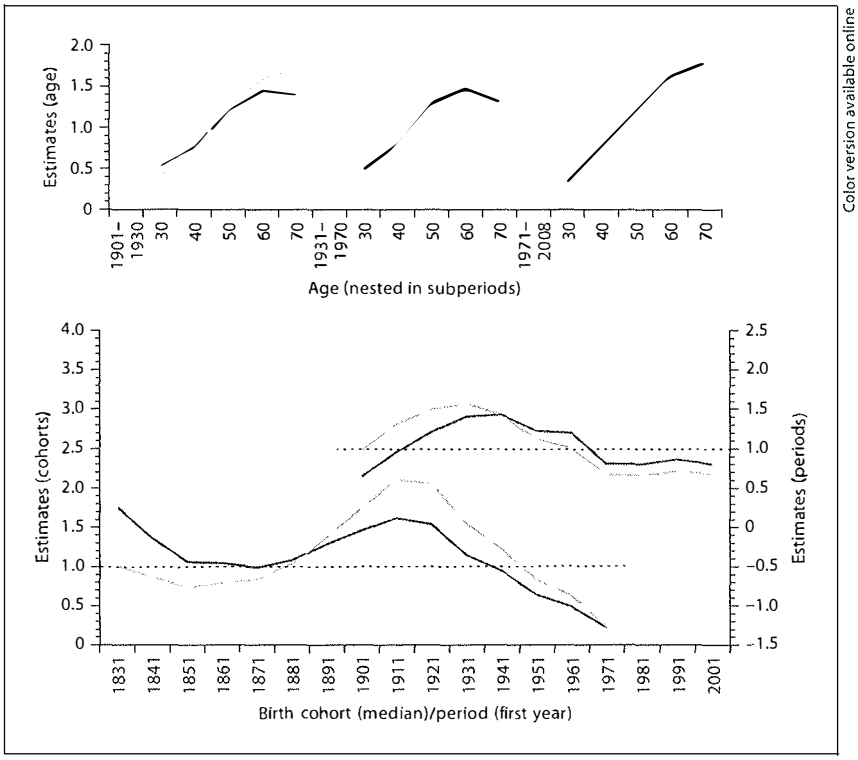

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Fig. 6. APC analysis of Swiss MS mortality data, 1901–2008: estimates of the main effect APC model (dashed line) and the A(p)PC model including nested effects (bold line).

due for example to prolongation of life expectancy [15, 38–40]. The results were not uniform and differed by country.

The APC analysis of Swiss ALS data also yielded equivocal results. While the APC model with main effects returned a slightly better model fit, the A(p)P model (age effects nested into three subperiods) was more parsimonious. This model also seems to be more appropriate in view of the age patterns in ALS (fig. 1). However, it remains to be seen whether further analyses will support this interpretation.

Parkinson's Disease

The study by Poskanzer and Schwab [24] in 1963 was the first to introduce the issue of birth cohort analysis in neuroepidemiology. It focused on the role of the encephalitis lethargica epidemics of the 1920s as a risk factor for PD, which could trigger PD not only in a direct but also in a delayed manner.

In this study, the birth cohort effects in PD smoothed out after nested age effects were included in the model. The change in age patterns was similar to that in ALS, even if the cause does not need to be the same. There are several hypothetical explanations: a prolongation of life expectancy in patients due to better treatment and care, a prolongation of life expectancy in diseases sharing the same risk factors (so that more persons get PD), a change in registration practice giving PD a higher registration priority. Finally, the birth cohorts born before the encephalitis lethargica epidemics carried the highest estimates.

Multiple Sclerosis

Many etiopathogenetic hypotheses in MS focus on the role of noxes, such as infectious diseases occurring in childhood or youth [41]. The latency period between the occurrence of risk factors and MS onset has been discussed in depth [42]. Therefore, and in addition to the indirect evidence deriving from changing rates and season of birth issues, it was not contradictory to encounter birth cohort trends in MS in this study.

Preliminary APC analyses [12], and analyses using a similar APC approach, which have been carried out with Swedish data [9], and also with Spanish data [10], have yielded similar results. Analyses using a descriptive approach [8] or regional data [11] have been less conclusive.

In Switzerland, the cohorts born around 1910–1920 carried the highest risk of MS throughout their lives. The background of these cohort effects is unclear, since none of the known risk factors [41, 43, 44] seems to be a suitable candidate in providing a plausible link for the interpretation: smoking, Epstein-Barr virus, other viruses, exposure to organic solvents, physical trauma, obesity and, finally, psychological distress. The same applies to suspected protective factors such as sunlight exposure/vitamin D, use of antibiotics and antihistamines, and dietary factors (such as n–3 polyunsaturated fat linoleic acid).

In contrast, the interpretation of period effects is somewhat easier. At the beginning of the 20th century, MS was doubtless underreported, which explains the low period estimates of that time [45]. The downward trend since the 1960s is most probably due to the improving life expectancy of MS patients, notably after the broad introduction of antibiotics in medical treatment.

Technical Remarks and Limitations

One of the peculiarities of APC analyses which are based on conventional cohort tables (age × period tables) is that the birth cohort effects provide only an approximate resolution. For example, in tables with 10-year age groups and 10-year periods (as used in this analysis), a single cell of the data matrix spans a cohort of 19 birth years. This means that the birth cohorts in the APC analysis overlap, i.e. represent in fact weighted moving averages, which results in smoothed estimates. This clearly limits the potential of APC analysis: it is not possible to make conclusions about eventual short-term fluctuations in birth cohort effects, for example generated by any extraordinary epidemics or other sudden changes in predisposing risk factors.

APC analysis of mortality data may be impeded by changing registration schemes which are a typical source of changing age patterns. The reasons may include the direct change of registration priorities among diseases with different age structures. They may also include the extension of registered causes of death (in Switzerland since 1995), thus giving new additional causes of death the chance to be encoded as the underlying cause of death. APC models including nested age effects are a useful approach in handling such issues.

Conclusions

Predisposing risk factors are a challenging issue in chronic diseases, among them neurological diseases such as MS, ALS and PD. In particular, predisposing risk factors which may change in historical terms are represented by generational change, or, in technical terms, by birth cohort effects in APC analysis. In this study, APC analysis yielded evidence for birth cohort effects in MS, in PD, but probably not in ALS. There are plausible hypotheses about the background of birth cohort effects in PD – the encephalitis lethargica epidemics in the 1920s – but no similar hypotheses with respect to MS.

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